Diagnostic use of abdominal ultrasound in detecting extrapulmonary TB/EPTB or lymphoma in a HIV-endemic region

by

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Declaration

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Format

This is a Publication-ready format manuscript. We are currently in the process of submitting it to Southern African Journal of HIV Medicine.

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Acronyms and Abbreviations

AFB:	acid-fast bacilli
ART:	antiretroviral therapy
CXR:	chest x-ray
EPTB:	extrapulmonary tuberculosis
GSH:	Groote Schuur hospital
HREC:	Human Research Ethics Committee
IQR:	interquartile range
LAM:	lipoarabinomannan
LDH:	lactate dehydrogenase
NPV:	negative predictive value
PPV:	positive predictive value
PACS:	Picture Archiving and Communication System
PLWH:	people living with HIV
RADLAC:	rapid access diagnostic lymphadenopathy clinic
WHO:	World Health Organization

Publication ready manuscript

Title

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Abstract

Background: Extrapulmonary tuberculosis (EPTB) is common among people living with HIV (PLWH). The abdominal ultrasound is an accessible investigation frequently employed to support the diagnosis of EPTB but may lead to misdiagnoses of diseases with overlapping clinical features, such as lymphoma.

Objectives: To describe the abdominal ultrasound features and confirmed diagnoses of patients referred to a biopsy clinic with unexplained lymphadenopathy.

Method: This was a retrospective descriptive study of patients attending the peripheral lymph node biopsy clinic at Groote Schuur Hospital (GSH) between 2017 and 2020 who had abdominal ultrasound examination while being investigated for unexplained lymphadenopathy. Ultrasound features were compared to the final diagnosis made on the lymph node biopsy.

Results: Thirty-four patients were included, most of whom were HIV-infected (59.0%). Approximately one third had a confirmed diagnosis of lymphoma (29%) and approximately one third had a confirmed diagnosis of tuberculosis (32%). Splenic hypoechoic lesions were more common in patients with lymphoma (63.6%) than patients with tuberculosis (45.5%) and malignancy (16.7%). Ascites was equally distributed between patients with tuberculosis (36.4%) and lymphoma (36.4%). The ultrasound report and confirmed diagnoses were in agreement in 40.0% of patients with tuberculosis. Additionally, 36.4% of patients with confirmed lymphoma were suspected to have tuberculosis based on the abdominal ultrasound.

Conclusion: Abdominal ultrasound detection of abnormalities such as splenic hypoechoic lesions, lymphadenopathy and ascites/pleural effusion have a differential diagnosis including both tuberculosis and lymphoma, and should be interpreted in conjunction with equally focused diagnostic tests.

Introduction

The estimated HIV prevalence is approximately 13,7% among the South African population. The total number of people living with HIV (PLWHIV) was estimated at approximately 8,2 million in 2021. Extrapulmonary tuberculosis (EPTB) is more common in PLWH and is difficult to diagnose due to the paucibacillary nature of the disease.[1, 2]

In addition, the diagnosis of EPTB in resource-limited settings is even more challenging. Without a proven diagnosis, physicians frequently turn to empiric or presumptive tuberculosis therapy in tuberculosis endemic areas.[3] The careful follow-up of patients on presumptive tuberculosis therapy and monitoring of their clinical response is important but is seldom done in a tuberculosis endemic setting.[4] Due to the high burden of patients with tuberculosis as well as diagnostic limitations, physicians frequently use a composite of clinical findings and insensitive investigation findings combined into a 'score' to diagnose EPTB.[5, 6]

Without close and expert follow-up, this practice may underdiagnose conditions that mimic tuberculosis and drug-resistant tuberculosis. Of particular concern is a missed diagnosis of a disease where timely diagnosis affects outcome, such as cancer. Cancer is the leading cause of death for PLWH in economically developed countries and Non-Hodgkin's lymphoma is the most common cancer in the United States.[7] The latest Global Cancer Observatory ranked lymphoma as the seventh most common cancer in South Africa.[6]

But there are several challenges in studying cancer prevalence in PLWH in South Africa and the true prevalence of lymphoma is unknown.[8] A study done more than a decade ago in a tertiary centre in Johannesburg, South Africa showed lymphoma has a 10-100 fold increased incidence in PLWH.[9]

Lymphoma has many overlapping features with EPTB including lymphadenopathy, fever, night sweats, weight loss and abnormal abdominal ultrasound features.[10, 11] In addition, cohorts of patients with lymphoma from tuberculosis-endemic areas, have up to 85% of patients on presumptive tuberculosis treatment at the time of lymphoma diagnosis.[12-14]

Abdominal ultrasound is an accessible investigation used frequently to support the diagnosis of tuberculosis, especially in PLWH. Common features suggesting EPTB seen on abdominal ultrasound are hepatomegaly, hepatic lesions,

lymphadenopathy, ascites, pleural effusions, splenomegaly and splenic hypoechoic lesions.[15] Splenic hypoechoic lesions on ultrasound are present in one out of five PLWH and their presence has, therefore, been suggested as a sufficient indication to initiate tuberculosis treatment in PLWH. [16]

PLWH not only have an increased risk for EPTB but also have an elevated risk of lymphoma . These patients more commonly present with extranodal lymphoma which involves organs such as the liver and spleen.[17] Splenic involvement of lymphoma occurs in 30-40% of Non-Hodgkin's and one third of Hodgkin's lymphomas.[18] Intra-abdominal lymphoma may frequently cause abdominal lymphadenopathy [17]. Ascites is less frequent in lymphoma, but may occur especially in PLWH who have a higher rate of extranodal disease.[17] Lymphoma is a commonly overlooked cause in the differential diagnosis of splenic hypoechoic lesions on ultrasound, due to the estimated 10 times higher incidence of tuberculosis compared to lymphoma in South Africa [6, 19] .

The aim of this study is to describe the abdominal ultrasound features among patients referred to a lymph node biopsy clinic with unexplained lymphadenopathy and to compare these features with their final diagnosis determined by a battery of tests including histology.

Research methods and design

Study design

This was a retrospective descriptive study. Study patients were identified from a cohort of patients referred to the rapid access diagnostic lymphadenopathy clinic (RADLAC) for lymph node biopsies from 1 November 2017 to 30 September 2020.

Setting

The study was located at the Clinical Haematology unit, Groote Schuur Hospital (GSH), a tertiary referral academic hospital in Cape Town, South Africa. GSH is one of the largest government-funded academic hospitals in South Africa, with approximately 900 beds, offering a wide variety of healthcare services.

Study population and sampling strategy

Study participants were selected from the RADLAC database if an abdominal ultrasound was done in their referring health care unit, as part of the work-up for unexplained lymphadenopathy, within six months of referral to RADLAC. The inclusion criteria for the RADLAC were adults (≥18 years), referred with lymphadenopathy (lymph node >20mm in the widest diameter) located in either the cervical, axillary or inguinal region. Patients on presumptive tuberculosis therapy were enrolled provided this had been given for less than one month. Patients with contraindications to core-needle biopsy (low platelets, other coagulopathy and bleeding risk, clinically unstable, site of biopsy unsafe) were excluded.

Data collection

As part of the routine enrolment of patients attending the RADLAC, demographic information, symptoms, symptom duration, physical findings, HIV status, blood results, and results of prior tuberculosis investigations performed, were recorded. The site of biopsy was recorded, along with other sites of lymphadenopathy. The presence and duration of constitutional symptoms (cough, loss of weight, night sweats, fever) were specifically enquired about, as was the duration of lymphadenopathy. Blood was taken for a full blood count with differential and lactate dehydrogenase (LDH) if not performed in the two weeks prior to lymph node biopsy. For all HIV-infected patients, a recent CD4 count, and viral load was collected for those on antiretroviral therapy (ART).

Abdominal ultrasound reports were obtained from the Picture Archiving and Communication System (PACS), which contains imaging data and reports from GSH as well as its referral hospitals. The ultrasounds were performed by sonographers, registrars and qualified radiologists employed at different hospitals. The findings on the abdominal ultrasound report were recorded and added to the existing Research Electronic Data Capture (REDCap) database that is used to capture data for the RADLAC. The parameters that were reviewed on the abdominal ultrasound reports were hepatomegaly, hepatic lesions, lymph node size and location, presence of ascites or pleural effusion, splenomegaly, splenic hypoechoic lesions, and the suspected diagnosis made by the ultra-sonographer.

Tests on lymph node specimens

In the RADLAC, fine-needle aspiration (using a 22-G needle and 5 mL syringe) was performed first to check for caseous material; if > 0.5 mL of caseous material was aspirated, the MTB/Rif Xpert Ultra assay, an air-dried smear for acid-fast bacilli (AFB) using the Ziehl-Neelsen stain and a tuberculosis culture were performed.[12] If < 0.5 mL of caseous material was aspirated, a core-biopsy was performed using an automated biopsy gun (BARD MagnumTM, CR Bard Inc., Covington, GA, USA) with a 14-G needle. The tissue was subjected to histological examination including AFB staining, as well as the MTB/Rif Xpert Ultra assay and tuberculosis culture. If all test results were inconclusive, the patient underwent either a repeat core-biopsy or an excision biopsy at the discretion of the treating clinician.[12] As already described in the RADLAC, focused investigations were carried out on lymph node tissue and aspirate to diagnose tuberculosis and lymphoma.[12] Tuberculosis was diagnosed on lymph node aspirate or tissue if AFBs were identified or if the culture or the Xpert MTB/RIF Ultra was positive. Bacterial adenitis was diagnosed if pus was aspirated, and all tuberculosis investigations were negative. Other diagnoses were made histologically on the core or excision biopsy. Lymphoma type was classified according to the 2016 World Health Organization (WHO) classification of lymphoma tissues.[20]

Data analysis

Data were analysed using STATA V14 (Stata Corporation, College Station, Texas, USA).[21] Categorical variables were described by frequencies and percentages, and compared using Pearson Chi-squared or Fisher's exact tests, as appropriate. Numerical variables were described by medians and interquartile ranges and compared using student's t-tests (parametric data) and Mann-Whitney or Kruskal Wallis tests (non-parametric data). In exploratory analysis presented as supplementary material, we calculated the diagnostic accuracy with 95% confidence intervals (sensitivity, specificity, positive predictive values, and negative predictive values) of selected individual and combined ultrasound features by comparing them to the composite reference standard of a histological, Xpert MTB/RIF Ultra or culture diagnosis. For all analyses statistical significance was set at $\alpha=0.05$.

Ethical considerations

Ethical approval for this study and the RADLAC were obtained from the University of Cape Town's Human Research Ethics Committee (HREC), of the Faculty of Health Sciences (HREC674/2017 and HREC830/2020). Informed consent was obtained from all participants in the RADLAC. This study was conducted in accordance with the Declaration of Helsinki.

Results

Of the 188 patients included in the RADLAC between November 2017 and September 2020, 34 (18.0%) patients had an abdominal ultrasound examination in their referring health care unit while being investigated for unexplained lymphadenopathy (Figure 1). Compared to those who did not have an abdominal ultrasound, the 34 patients who underwent abdominal ultrasound examination were significantly more likely to undergo chest x-ray (CXR) examination in their referring health care unit, (91.0% versus 38.0%, $P<0.001$). Patients who had an abdominal ultrasound also had a significantly lower haemoglobin (median 10.3 g/dL versus 12.4 g/dL, $P<0.001$) and a higher proportion of axillary and inguinal lymphadenopathy (axillary: 17.6% vs 7.1%; inguinal: 8.8% vs 2.0%, $P = 0.014$), but a lower proportion of cervical lymphadenopathy (73.5%) compared to their counterparts (90.9%). There were no further significant differences between those who had an abdominal ultrasound and those who did not. Additional information on the 154 patients without an abdominal ultrasound is presented in Supplementary Table 1.

Most patients were HIV-infected (59.0%) and the median age of the cohort was 33 years (Table 1). Among PLWH, 13 (65.0%) were on ART at the time of lymph node biopsy, 5 of whom were virally supressed. The median CD4 count was 113.5 cells/mm^3 (IQR 68 – 292). The most common biopsy site was the neck (73.5%). The median haemoglobin was significantly lower among PLWH compared to their counterparts ($P = 0.013$). There was no significant difference between median haemoglobin by diagnostic outcome ($P = 0.473$). The most common indication for an abdominal ultrasound was suspected EPTB (17/34 cases: 50.0%). Suspected lymphoma was only reported as the indication for ultrasound in three cases. The distribution of diagnostic outcomes is presented in Figure 2.

Approximately one third of patients had a final diagnosis of lymphoma (29%) and approximately one third of patients had a diagnosis of tuberculosis (32%).

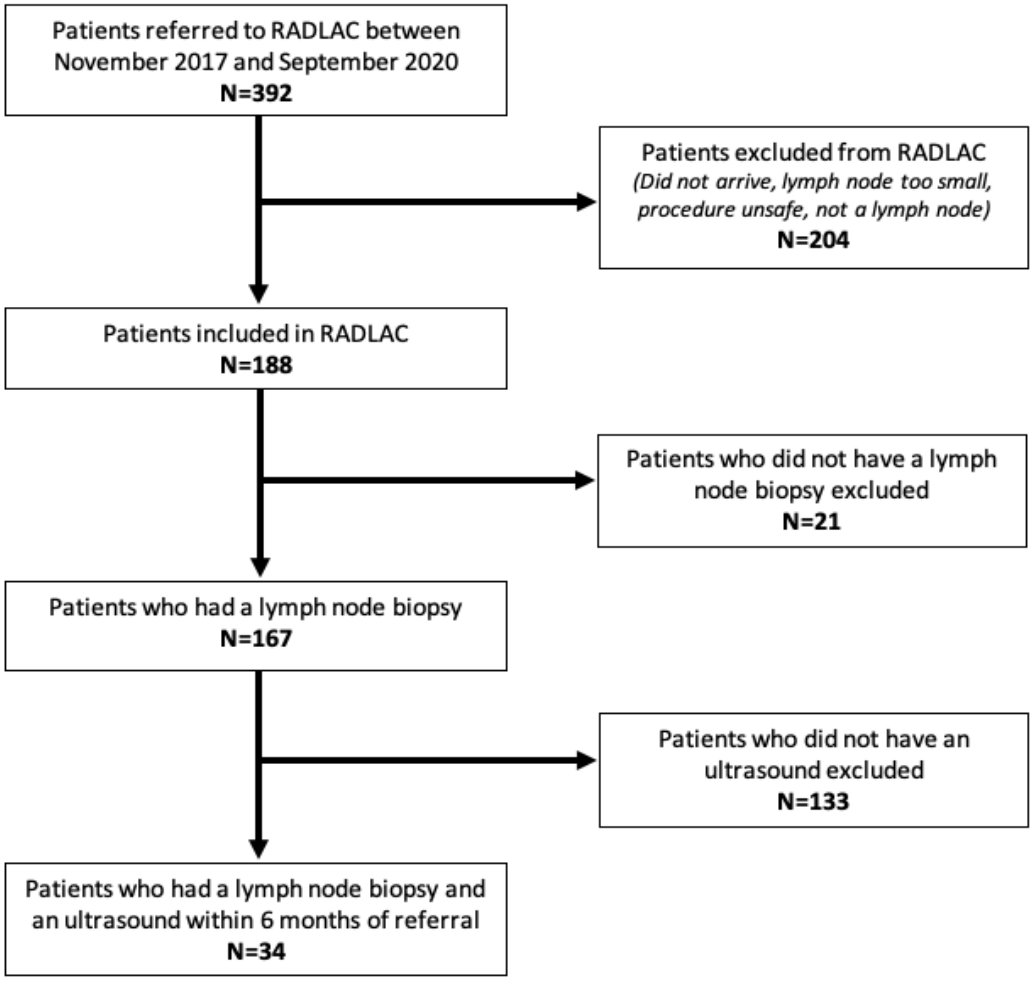

Figure 1: Consort diagram of patients included in this study.

Table 1: Demographic and clinical characteristics of patients with a lymph node biopsy and abdominal ultrasound between 2017 and 2020.

Variable	**Total (n = 34)** *n* (%) or median (IQR)	**HIV+** *n* = 20 (59%)	**HIV-** *n* = 14 (41%)
Age at presentation	33.2 (28.5 – 43.2)	32.5 (28.9 – 37.8)	37.0 (28.4 – 61.8)
Males	13 (38.2)	8 (40.0)	5 (35.7)
Blood results			
Haemoglobin (g/dL)	10.3 (6.5 – 12.2)	8.2 (6.3 – 11.2)	11.8 (10.8 – 13.6)
Lymphocytes (x 10^9/L) (n = 28)	1.5 (0.8 – 2.2)	0.9 (0.7 – 1.7)	1.8 (1.1 – 2.4)
Platelets (x 10^9/L) (n = 33)	337 (265 – 422)	286 (106 – 510)	347 (290 – 403)
LDH (U/L) (n = 29)	270 (191 – 340)	262 (201 – 340)	272 (183 – 343)
Constitutional symptoms present	25 (73.5)	14 (70.0)	11 (78.6)
CXR performed before biopsy	31 (91.2)	20 (100.0)	11 (78.6)
Lymph node site			
Neck	25 (73.5)	15 (75.0)	10 (71.4)
Axillary	6 (17.6)	3 (15.0)	3 (21.4)
Inguinal	3 (8.8)	2 (10.0)	1 (7.1)
Final diagnosis			
Tuberculosis	10 (29.4)	5 (25.0)	5 (35.7)
Lymphoma	11 (32.4)	8 (40.0)	3 (21.4)
Other malignancy	6 (17.7)	5 (25.0)	1 (7.1)
Other	5 (14.7)	1 (5.0)	4 (28.6)
Inconclusive*	2 (5.9)	1 (5.0)	1 (7.1)

Abbreviations: LDH = lactate dehydrogenase, CXR = chest x-ray, IQR = interquartile range ;* Final diagnosis described as inconclusive if no ultrasound diagnosis was indicated on the ultrasound report

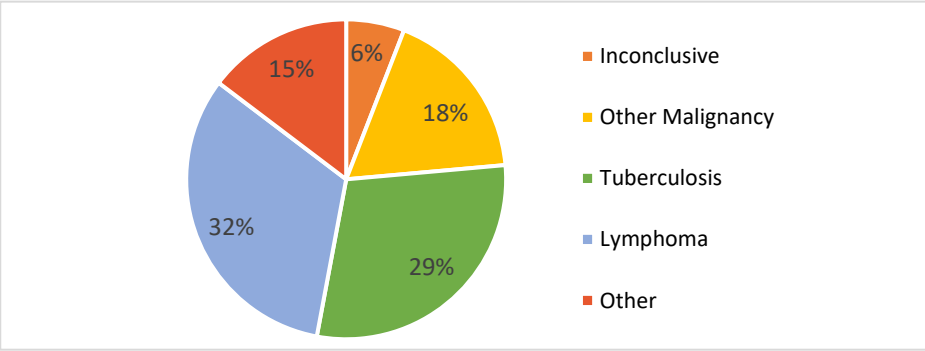

Figure 2: Distribution of diagnostic outcomes.

Table 2 describes the diagnostic relationship between the confirmatory testing (histology, microscopy, culture, cytology, Xpert MTB/RIF Ultra) and the suspected diagnosis on abdominal ultrasound. The finding on the ultrasound report was "inconclusive" in most cases (*n* = 20; 58.8%) and lymphoma was never suspected as the diagnosis. The ultrasound report was deemed inconclusive, when no diagnosis was suggested on the report by the reporting clinician. The ultrasound report and the confirmed diagnosis were in agreement in only 40.0% of patients with tuberculosis. Additionally, 36.4% of patients with confirmed lymphoma were suspected to have tuberculosis based on the abdominal ultrasound. At the time of attending the RADLAC, 13 patients (38.2%) were on empiric tuberculosis therapy. Of these, only 5 patients had a final diagnosis of tuberculosis, while the others were diagnosed with Lymphoma (n=5), Malignancy (n=1) and Reactive lymphadenopathy (n=2).

Table 2: Diagnostic relationship between abdominal ultrasound findings and confirmed diagnosis from lymph node biopsy (histology, microscopy, culture, cytology, Xpert MTB/RIF Ultra).

		Confirmed diagnosis from lymph node biopsy n (%) (histology, microscopy, culture, cytology, Xpert MTB/RIF Ultra)				
		Tuberculosis (*n* = 10)	**Lymphoma** (*n* = 11)	**Malignancy** (*n* = 6)	**Other*** (*n* = 5)	**Inconclusive** (*n* = 2)
Suspected diagnosis based on abdominal ultrasound	**Tuberculosis (*n* = 11)**	4 (40.0)	4 (36.4)	1 (16.7)	2 (40.0)	0 (0.0)
	Lymphoma (*n* = 0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Malignancy (*n* = 1)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
	Other (*n* = 2)**	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (50.0)
	Inconclusive^{+} (*n* = 20)***	6 (60.0)	6 (55.6)	4 (66.7)	3 (60.0)	1 (50.0)

$^{+}$Final diagnosis described as inconclusive if no ultrasound diagnosis was indicated on the ultrasound report

*other biopsy diagnoses included: 3 reactive, 1 sarcoidosis, 1 sinus histiocytosis

**the 2 other diagnoses made on ultrasound were gallstones

*** Of the 20 inconclusive abdominal ultrasounds, 18 had abnormalities present, while 3 were normal

Regarding specific ultrasound findings presented in Table 3, splenic hypoechoic lesions (46.4%) and lymphadenopathy (42.9%) were most commonly reported. Splenomegaly was not present in patients with tuberculosis and present in 36,4% of lymphoma patients. Hepatic lesions (3.6%) were the least common ultrasound finding. Splenic hypoechoic lesions were more common in patients with lymphoma (63.6%) compared to patients with tuberculosis (45.5%) and malignancy (16.7%). Lymphadenopathy was most often found in lymphoma patients (63.6%), followed by patients with malignancy (50.0%) and tuberculosis (18.2%). Ascites was equally distributed between patients with tuberculosis (36.4%) and lymphoma (36.4%).

Table 3: Abdominal ultrasound findings present among patients diagnosed with tuberculosis, lymphoma, or malignancy on lymph node biopsy.

		Lymph node biopsy diagnosis (histology, microscopy, culture, cytology, Xpert MTB/RIF Ultra) ***n* (%)**		
		Tuberculosis (*n* = 11)	**Lymphoma** (*n* = 11)	**Malignancy** (*n* = 6)
Abdominal ultrasound finding	Hepatomegaly (*n* = 6; 21.4%)	2 (18.2)	3 (27.3)	1 (16.7)
	Hepatic lesions (*n* = 1; 3.6%)	0 (0.0)	0 (0.0)	1 (16.7)
	Lymphadenopathy (*n* = 12; 42.9%)	2 (18.2)	7 (63.6)	3 (50.0)
	Ascites (*n* = 9; 32.1%)	4 (36.4)	4 (36.4)	1 (16.7)
	Pleural effusion (*n* = 6; 21.4%)	3 (27.3)	1 (9.1)	2 (33.3)
	Splenic hypoechoic lesions (*n* = 13; 46.4%)	5 (45.5)	7 (63.6)	1 (16.7)
	Splenomegaly (*n* = 6; 21.4%)	0 (0.0)	4 (36.4)	2 (33.3)
	3 features present (lymphadenopathy, ascites/pleural effusion & splenic hypoechoic lesions) (*n* = 5; 17.9%)	2 (18.2)	3 (27.3)	0 (0)

Discussion

This study aimed to provide a descriptive analysis of abdominal ultrasound findings in patients who were investigated for lymphadenopathy, and to compare these features to their confirmed lymph node biopsy diagnosis. The novelty of this small pilot study is the use of both histology and Xpert MTB/RIF Ultra as part of the battery of diagnostic tests. Our study highlights that there are overlapping radiological features between tuberculosis and lymphoma. In a tuberculosis endemic area, it is important to confirm the diagnosis of tuberculosis. In the context of patients started on empirical tuberculosis therapy, patients should be followed up and monitored for the improvement of symptoms and weight gain. Patients with persistent lymphadenopathy and constitutional symptoms on empirical tuberculosis therapy, should be referred for urgent biopsy and histological diagnosis. In settings where a lymph node biopsy is not possible an Xpert MTB/RIF Ultra on needle aspirates of lymph nodes has been shown to perform well and can confirm tuberculosis without a biopsy.

The use of abdominal ultrasound to aid diagnosis of EPTB has been widely described [15, 16]. A systematic review evaluating the ultrasound features of PWLH with tuberculosis coinfection in five countries including, developed and developing countries, showed that splenic hypoechoic lesion were present in 62.5% of patients.[16] In contrast, our study compared multiple ultrasound features in HIV-infected and HIV-uninfected patients with tuberculosis or histological proven lymphoma in South Africa. Our study found a lower frequency of splenic hypoechoic lesion in patients with tuberculosis (45.5%). Additionally, splenic hypoechoic lesions were more common in patients with lymphoma (63.6%) compared to patients with tuberculosis. Moreover, the presence of splenomegaly seems to be the best discriminator between tuberculosis and lymphoma as this feature was not present in any patients with tuberculosis and was present in 36,4% of lymphoma patients.

Griesel et al, conducted a prospective study of HIV-infected inpatients, with WHO danger signs and cough, in a South African hospital. [22] They examined multiple ultrasound features among PLWH and tuberculosis co-infection. Their most prominent finding was that the combination of three ultrasound features (ascites/pleural effusions, lymphadenopathy and splenic hypoechoic lesions) was highly specific for diagnosing tuberculosis. They noted that all three features were

present in 11% of their cohort. In our study, the combination of these three features was present in 18.2% of tuberculosis patients and 27.3% of lymphoma patients. In exploratory analysis (Supplementary Table 2), we found that the combined presence of lymphadenopathy, ascites and splenic hypoechoic lesions on abdominal ultrasound had equally high specificity and low sensitivity for detecting both tuberculosis and lymphoma. Even though tuberculosis is estimated to be 10 times more prevalent than lymphoma in the South African setting, in our study the combination of these features was not pathognomonic of tuberculosis.

Possible discrepancies between our findings and the above studies may be due to the use of different reference standards, different abdominal ultrasound criteria and different populations. Our study included HIV-infected and uninfected individuals and we used multiple diagnostic tests including histology, microscopy, culture, cytology and Xpert MTB/RIF Ultra. Studies included in the systematic review did not all make use of newer tuberculosis diagnostic tests such as the Xpert MTB/RIF Ultra and largely did not carry out proper histological confirmation of available tissue for exact diagnosis, including lymphoma. This may have ultimately resulted in misdiagnosis of patients. Nonetheless, we suggest that abnormal findings noted on an abdominal ultrasound should prompt more focused investigational techniques to confirm a diagnosis and facilitate appropriate treatment and patient management. Additional investigations might include flow cytometry on pleural or ascitic fluid to assess for a clonal lymphoid population, or an ultrasound guided intra-abdominal lymph node biopsy if there is not an accessible peripheral lymph node.

The main strength of this study is the use of a stringent reference standard (histology, microscopy, culture, cytology, Xpert MTB/RIF Ultra) as the comparator to ultrasound findings. Additionally, biopsies were done in a single centre and performed by a single clinician. The major limitation of this study was the highly selected population of patients referred for unexplained lymphadenopathy**,** presumably after other investigations were inconclusive. This may have enriched for lymphoma. Secondly, the sample size was small. This may have reduced precision and ultimately resulted in study that was underpowered to evaluate the diagnostic accuracy. Additionally, the procurement of ultrasound reports was retrospective and since four different hospitals formed part of the referral pathway, standardizing ultrasound reporting could not be guaranteed. Finally, all participants had an

accessible peripheral lymph node, therefore, our findings may not be generalisable to patients with tuberculosis or lymphoma without the presence of peripheral nodes.

Conclusion

Abdominal ultrasound is widely used to support the diagnosis of EPTB in tuberculosis endemic areas. Our findings suggest that the ultrasound should not be used to reliably differentiate between lymphoma and tuberculosis as they have overlapping radiological features on abdominal ultrasound. The utility of ultrasound should be to identify patients who are at high risk of having either tuberculosis or lymphoma and to prompt further investigation to confirm the diagnosis. Patients not responding to empiric tuberculosis therapy, should be referred early for lymph node biopsy. Due to the selection bias of our study population , it's difficult to extrapolate our findings to other populations. Further research is required to refine the diagnostic pathways and prevent inaccurate and late diagnosis.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author contributions

Prof Estelle Verburgh conceptualised the study. Dr Ellouise Chantel Adams reviewed the ultrasound reports, collected data and wrote the article. Jenna Oosthuizen and Karryn Brown assisted with data management and performed the statistical analysis. Dr Katherine Antel, Prof Vernon Louw and Prof Gary Maartens reviewed and corrected the final manuscript. All authors discussed the results and contributed to the final manuscript.

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Data availability

Raw data were generated at Groote Schuur Hospital. Derived data supporting the findings of this study are available from the corresponding author Dr Ellouise Chantel Adams on request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agenda of the authors.

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Supplementary Table 1: Demographic and clinical characteristics of patients with a lymph node biopsy and without an abdominal ultrasound between 2017 and 2020

Variable	**Total (N = 154)** *n* (%) or median (IQR)	**HIV+** *n* = 63 (41%)	**HIV-** *n* = 91 (59%)
Age at biopsy	36.5 (28.7 – 49.2)	35.6 (31.0-42.6)	37.8 (26.0-54.9)
Sex			
Female	74 (48.1)	31 (49.2)	43 (47.3)
Male	80 (52.0)	32 (50.8)	48 (52.8)
Blood results			
Haemoglobin (g/dL) (n = 150)	12.4 (10.6 – 13.8)	11.8 (9.2 – 13.1)	13.0 (11.7 – 14.1)
Lymphocytes (x 10^9/L) (n = 150)	1.8 (1.1 – 2.5)	1.6 (0.9 – 2.3)	2.0 (1.4 – 2.7)
Platelets (x 10^9/L) (n = 149)	333 (247 – 413)	315 (228 – 430)	349.5 (278 – 412.5)
LDH (U/L) (n = 131)	250 (212 – 318)	262.5 (227 – 328)	238(196 – 299)
Constitutional symptoms present	92 (59.7)	37 (58.7)	55 (60.4)
CXR performed before biopsy	59 (38.3)	20 (31.8)	39 (42.9)
Lymph node site			
Neck	140 (90.9)	58 (92.1)	82 (90.1)
Axillary	11 (7.1)	5 (7.9)	6 (6.6)
Inguinal	3 (2.0)	0 (0.0)	3 (3.3)
Final diagnosis			
Tuberculosis	57 (37.0)	30 (47.6)	27 (29.7)
Lymphoma	37 (24.0)	17 (27.0)	20 (22.0)
Malignancy	25 (16.2)	1 (1.6)	24 (26.4)
Other	28 (18.2)	12 (19.1)	16 (17.6)
Inconclusive	7 (4.6)	3 (4.8)	4 (4.4)

Abbreviations: LDH = lactate dehydrogenase, CXR = chest x-ray, IQR = interquartile range

Supplementary Table 2: **Diagnostic accuracy of individual and combined abdominal ultrasound features among patients diagnosed with lymphoma or tuberculosis.**

Abdominal ultrasound feature	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lymphoma				
Lymphadenopathy	63.6 (30.8-89.1)	73.9 (51.6-89.8)	53.8 (25.1-80.8)	81.0 (58.0-94.6)
Ascites/Pleural effusion	36.4 (10.9-69.2)	56.5 (34.5-76.8)	28.6 (8.4-58.1)	65.0 (40.8-84.6)
Splenic hypoechoic lesions	63.6 (30.8-89.1)	60.9 (38.5-80.3)	43.8 (19.8-70.1)	77.8 (52.4-93.6)
Any 1 or more features present	90.9 (58.7-99.8)	30.4 (13.2-52.9)	38.5 (20.2-59.4)	87.5 (47.3-99.7)
Any 2 or more features present	45.5 (16.7-76.6)	69.6 (47.1-86.8)	41.7 (15.2-72.3)	72.7 (49.8-89.3)
3 features present	27.3 (6.0-61.0)	91.3 (72.0-98.9)	60.0 (14.7-94.7)	72.4 (52.8-87.3)
Tuberculosis				
Lymphadenopathy	20.0 (2.5-55.6)	54.2 (32.8-74.4)	15.4 (1.9-45.4)	61.9 (38.4-81.9)
Ascites/Pleural effusion	60.0 (26.2-87.8)	66.7 (44.7-84.4)	42.9 (17.7-71.1)	80.0 (56.3-94.2)
Splenic hypoechoic lesions	50.0 (16.7-76.6)	54.2 (32.8-74.4)	31.3 (11.0-58.7)	72.2 (46.5-90.3)
Any 1 or more features present	70.0 (34.8-93.3)	20.8 (7.1-42.2)	26.9 (11.6-47.8)	62.5 (24.5-91.5)
Any 2 or more features present	40.0 (12.2-73.8)	66.7 (44.7-84.4)	33.3 (9.9-65.1)	72.7 (49.8-89.3)
3 features present	20.0 (2.5-55.6)	91.7 (73.0-99.0)	50.0 (6.8-93.2)	73.3 (54.1-87.7)

Abbreviations: PPV = positive predictive value, NPV = negative predictive value

Appendices:

Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 December 2020

HREC REF: 830/2020

A/Prof E Verburgh
Division of Clinical Haematology
E5, Haematology, NGSH
Email: estelle.verburgh@uct.ac.za
Student: ellouiseadams@gmail.com

Dear A/Prof Verburgh

PROJECT TITLE: A RETROSPECTIVE CROSS-SECTIONAL STUDY OF THE ABDOMINAL ULTRASOUND FINDINGS OF PATIENTS EVALUATED FOR PERIPHERAL LYMPHADENOPATHY IN A HIGH HIV TB ENDEMIC POPULATION-MMED CANDIDATE-DR ELLOUISE ADAMS-sub-study linked to 674/2017

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 December 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Ellouise Adams will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC/REF 830/2020sa

Groote Schuur Hospital Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail:GSHReserach.Request@westerncape.gov.za

Professor Estelle Verburgh
MEDICINE - HAEMATOLOGY

E-mail: Estelle.Verburgh@uct.ac.za

Dear Professor Verburgh,

RESEARCH PROJECT: A Retrospective Cross-Sectional Study Of The Abdominal Ultrasound Findings Of Patients Evaluated For Peripheral Lymphadenopathy In A High HIV TB Endemic Populations (MMed Dr Ellouise Adams)(Sub-study Linked to 674/2017)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until 30 December 2021.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 9 March 2021

C.C. Mr. L. Naidoo / Professor N. Ntusi / Professor V. Louw

G46 Management Suite, Old Main Building,
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Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Department Research Committee Approval

DIVISION OF CLINICAL HAEMATOLOGY, DEPARTMENT OF MEDICINE
CLINICAL RESEARCH OFFICE
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Groote Schuur Hospital
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Cape Town, South Africa
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E-mail Research Coordinator: jenna.oosthuizen@uct.ac.za
E-mail Research Supervisor: estelle.everburgh@uct.ac.za
E-mail Head of Division: vernon.louw@uct.ac.za

PROTOCOL COVER PAGE

1. Protocol application form
2. Synopsis
3. Motivation for expedited review
4. Research protocol
5. Memorandum of understanding
6. Appointment of supervisor
7. Departmental research proposal checklist

FHS013: New protocol application form – Section A

Instructions

Researchers must ensure that they use the current version of the application form on UCT Administrative Forms web page.

- Applicants wishing to register **databases, registries** or **repositories** should only fill out form FHS020.

1. Protocol information

Protocol title	A retrospective cohort study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a high HIV TB endemic population
Protocol number (if applicable)	

Is this a sub-study or an extension study linked to an existing/main study previously approved by this Committee? (e.g. a sub-study, follow-up study, earlier phase trial) (tick √)	Yes [X]		☐ No	
If yes above, please provide the following with regards to the existing/main study:	HREC ref. no.	674/2017	Expiry approval date of existing/main study	30/11/2021

* Please comment briefly on safety and efficacy findings of the existing/main study that may have relevance to this application. (Please also add a brief description in new study synopsis)

The existing/main study supplies a database including patients with peripheral lymphadenopathy that's underwent a lymph node biopsy .The new study will review the cohort of patients that's received an abdominal ultrasound during their diagnostic pathway for peripheral lymphadenopathy .

2. Investigator(s) profile

Note:
- For all postgraduate student research, the **main** supervisor must be listed as PI on this form.
- For all undergraduate student research please **only** complete the FHS021 form and not this form.
- The PI or Co-PI **must** be a UCT affiliated person.

2.1 UCT's principal investigator (PI)

Title, first name, surname	Professor Estelle Verburgh
Department/Division	Hematology
Phone	0214043070
Email address	Estelle.verburgh@uct.ac.za
Department /Office Internal Mail Address for Correspondence	Estelle.verburgh@uct.ac.za

Registration with HPCSA (tick ✓)	✓ Yes	☐ No	Registration #	0368431	Expiry date	March 2021
Is the PI covered by professional liability insurance? (tick ✓)				Yes	✓ No	
If Yes above, please provide the liability insurance number and expiry date			Liability insurance #		Expiry date	

Note: **If a non-medically trained PI is overseeing research that involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator.**

2.2 Co-investigator(s) Note: Staff and students involved in the research must be listed as co-investigators

Title, first name, surname	Department/Division	Email
Ellouise Adams	Internal Medicine	ellouiseadams@gmail.com

2.3 Is this protocol for degree purposes? (tick ✓)

✓ Yes	☐ No

If yes, please specify:

Type of degree	MMed Internal medicine
Student's title, first name, surname	Dr Ellouise Adams
Student's email	ellouiseadams@gmail.com

2.4 Supervisor(s)

Title, first name, surname	Department and University	Email
Prof Estelle Verburgh	Hematology/Medicine UCT	Estelle.verburgh@uct.ac.za

2.5 How many of the following does the PI or supervisor currently oversee?
(Total number for all research projects)

Open research studies	7	Sites (excluding this application)	0

Co-investigators	3	Number of participants	0

2.6 What is the PI's role in authoring this protocol? (tick ✓ all relevant)	
Primary author	
Collaborator	
Supervisor	✓
None (developed by sponsors)	

2.7 Are there any publication restrictions on the research?	
☐ Yes	✓No
If yes, please describe and justify:	
NA	

2.8 Does the protocol comply with UCT's intellectual property rights policy? (tick ✓)		
Yes	X	☐ No
If no, please justify:		

3. Protocol profile

3.1 Has this protocol been submitted to another Human Research Ethics Committee? (tick ✓)		
☐ Yes		No X
If yes, please complete:	Name of Institution	Outcome

3.2 To your knowledge, has this protocol been rejected by another HREC? (tick ✓)			
☐ Yes	No X		☐ Don't know
If yes, please provide the reasons:			

3.3 Is there any vulnerability associated with the proposed participant groups?
Note: Group vulnerability refers to any potential vulnerabilities relating to pre-existing physiological or health conditions; cognitive or emotional factors; and socio-economic or legal status.

✓ Low	☐ Medium	☐ High

Please explain the group vulnerability and justify the need for research in this group of participants.

Secondary data analysis and retrospective review of patient records .

3.4 Please specify the level of risk associated with the proposed research.

Note: Research risk refers to the probability and magnitude of harms participants may experience as a result of the proposed research methods and/or type of data to be collected. Examples include research procedures or collection of data relating to clinical diagnoses or side effects; cognitive or emotional factors such as stress or anxiety during data collection; and socio-economic or legal consequences of research such as stigma, loss of employment, deportation, or criminal investigation.

✓Low	☐ Medium	☐ High

Please explain the research risk and justify the need for the proposed research.

The study method is a retrospective cohort study with low risk .

3.5 Is this study suitable for an expedited review? I.e. is the research considered to be minimal risk? (tick ✓)

✓ Yes	☐ No

If yes, please provide a motivation for expedited review:

This study is minimal risk and involves secondary data analysis and retrospective data review .No interactions with patients .

Note: **AT THE DISCRETION OF THE HREC CHAIRPERSON OR DESIGNATE, STUDIES UNDERGOING EXPEDITED REVIEW MAY NEED TO BE CONSIDERED AT A FULL COMMITTEE MEETIN**

3.6 Are there additional requirements by a funder or sponsor that require the study to undergo Full Committee review? (tick ✓)

☐ Yes	✓ No

Comments

3.7 Does this protocol comply with all the principles of the Helsinki Declaration of 2013, including care after research, if applicable? (tick ✓)	
✓ Yes	☐ No
If no, please explain with full justification:	

3.8 Is this a protocol for which insurance for research-related bodily injury would be appropriate? (tick✓)	
☐ Yes	✓ No (If 'no', please complete 3.8.4 below)

3.8.1 If 'yes', please indicate the type of insurance cover:		
☐ ABPI-compliant sponsor's insurance policy		☐ UCT No-Fault insurance policy
Insurer's name		
Policy no		
Coverage period		

Note: Please use the approved HREC Insurance Clause in your Consent Form as per the HREC SOP.

3.8.2 If UCT No-Fault insurance is required, please indicate if the study involves any of the following:		
☐ Pregnant women	☐ Minors	☐ Participants outside South African borders
If UCT No-fault insurance is required for participants outside South African borders, please specify the countries below:		

3.8.3 If the research will involve participants outside South African borders and these participants are not insured by a sponsor or local mechanism in that country, please specify the study site(s):

3.8.4 If no insurance for research-related bodily injury is required, please justify by indicating the type/nature of the proposed research:
☐ Qualitative research study ☐ Purely observational study ✓ Patient folder or document review only ☐ Questionnaires/Interviews only ✓ Study involves secondary data analysis only ☐ No human participants involved in the research study ☐ Other
If other, please specify:

4. Funding and grant information (Required)

Note: A summary budget must be attached in the appendices

4.1 Funding source	(tick ✓ at least one)	Ethics Review Levy – cost including vat
a. UCT (e.g. departmental funding / student research)	✓	R 0
b. New Clinical Trial Application		R 31993
c. International grant funded research (Total project budget above R5m)		R 22470
d. International grant funded research (Total project budget R1m to R5m)		R 14980
e. International grant funded research (Total project budget below R1m)		R 7490
f. National grant funded research (Total project budget >R1m)		R 3600
g. Extension clinical study / Additional clinical site		R 15000

Please complete the Ethics Debit form if you ticked off between b - g.

Note: **The HREC or its admin staff, do not have the authority to waive the ethics review levy. If a waiver is required, please contact Mr Salie Nassiep, the Research Management Accountant in the Faculty of Health Sciences** (021 406 6409) email: salie.nassiep@uct.ac.za

4.2 What is the total sponsorship/funding for this protocol?	

4.3 Into what entity will the funding be paid and when?	

4.4 Where applicable, has the PI negotiated an agreement with the hospital or other health or laboratory services to cover the costs of interventions/ procedures/ investigations performed solely for research purposes? (e.g. extra MRIs, CT scans, diagnostic tests, prolonged hospitalisation, use of non-research staff to collect research-related data or perform research-related procedures) **(tick ✓)**		
✓N/A	☐ Yes	☐ No
If no, please explain how research costs will be recovered		

5. Characteristics of the protocol

5.1 Category of research Please select an appropriate category for your protocol. If the protocol falls in more than one category, please designate a primary and secondary category by entering a '1' and a '2'.	
Medical intervention/ clinical trial (e.g. medicines, traditional or complementary medicines, nutriceuticals, devices or innovation)	
Behavioural/ psychosocial interventions (e.g. comparison of counselling programmes)	
Epidemiology/ observational study (e.g. survey, prevalence, case control, cohort studies)	✓
Quality improvement	
Testing new technologies	
Medical record review, audit	✓
Establishment of a specimen repository, medical data base/ registry	
Clinical laboratory studies	
Clinical laboratory studies (DNA related)	
Qualitative research (e.g. focus groups, in-depth interviewing, ethnography)	
Pilot study	
Other. Please describe:	

5.2 BIOHAZARD STATEMENT

Important: **All researchers must be aware of and familiar with the MDSS Safety Sheets for each of the compounds/organisms used in this study.**

Note: Faculty Biosafety Committee approval is required for all projects involving biohazardous material that poses a real or potential risk to human health and/or the environment.

Examples include: transfer of rDNA, DNA, or RNA into whole animals or plants; use of human or animal pathogens (BSL2 and higher); use of genes encoding toxins that are lethal for vertebrates; and release of GMOs into the environment.

Will this application require **approval** by the **Faculty Biosafety Committee?** If yes, please note that you are required to submit an application for approval to the Faculty Biosafety Committee / GMO committee. Please consult the Faculty Research webpage at: http://www.health.uct.ac.za/fhs/research/faculty-biosafety-committee	☐ Yes	✓No

5.3 Does the study involve innovative therapy? Innovative therapy is a newly introduced or modified therapy with unproven effect or side effect and is being delivered in the best interest of the patient. While there are clear distinctions in the aims of research and care, innovative therapy is experimental in nature and may involve data collection, similar to that for research. The HREC needs to determine whether the planned intervention can be classed as research.	☐ Yes	✓ No

Please describe the innovative therapy.

5.4 Category of participants	✓Adults	☐ Minors (<18 years)	
		Please specify age range:	

5.5 If conducting research with minors, please provide the justification for the proposed inclusion of minors in the study. (Required)			
5.5.1 Is the research considered 'non-therapeutic' i.e. does not have a likelihood of direct benefit to the minor participants?	☐ Yes	☐ No	✓N/A
For "Non-therapeutic" health research with minors, as part of the statutory requirements, Form A (NHREC Operational Guidelines for Ministerial Consent: v19 Feb 2015) must be completed and must accompany the FHS013 form. **Non-therapeutic research** is classified as research that includes interventions that do not hold the prospect of direct health-related benefit to the participant but may produce results that contribute to generalisable knowledge. (Please see SOP)			

5.6 Estimated number of participants to be enrolled at the local site.	Number of Adults:	50	Number of Minors:	

5.7 Estimated duration of the study.	2020-2021

5.8 Location(s) of the study: (Please supply name of the Research Unit / Site and/or Hospital/Institution and particular department – if applicable)

Groote Schuur hospital Clinical Hematology department

5.9 Which authority will be approached for institutional approval?
Note: Institutional approval/permission must be obtained before study commencement and must be obtained from the institution where the research data is being collected e.g. Hospital, School, Clinic, Department of Education, Provincial Department etc. prior to starting the project.

Groote Schuur hospital

5.10 Please describe where and how recruitment will take place; and who will be recruited?

Patients identified from an existing RedCap database linked to the lymph node biopsy clinic .

5.11 Who will be responsible for recruiting participants in this study?

Note: If the clinician involved in standard of care will be involved in this study and the recruitment of participants, please explain how the potential for therapeutic misconception will be minimized or avoided.

Data will be obtained from REDCap data base and hospital PACS system by Dr E Adams .

Note:

- **If including UCT staff:** Please obtain permission from Ms. Minam Hoosain, the Executive Director of Human Resources, when including UCT staff as research participants. (This is a University-wide requirement): Use forms HR194 and HR190.
- **If including UCT students:** Please obtain permission from Dr Mocnira Khan, the Executive Director, Department of Student Affairs when including students as research participants. (This is a University-wide requirement): Use form DSA 100

5.12 Will non-English speaking/non-English fluent participants be enrolled in the study? (tick ✓)		
☐ Yes	☐ No	✓N/A
If Yes, please **tick** ✓ what measures will be used to promote participants' and families' understanding:		

Written translation of consent/assent forms into a local language?	Afrikaans	IsiXhosa	☐ Other (specify):
Use of trained translator(s)/ interpreter(s)			
Other. Please specify below and describe how the investigators intend to explain the study to potential participants and ensure their understanding:			

5.13 Will human tissue samples be collected for research purposes?	☐ Yes	No X

5.13.1 Type of samples to be collected:

☐ Blood	☐ Tissue	☐ Genetic material	☐ Other (please specify in field below)

5.14 Will data and/or samples be stored for future use?	Yes	✓No
5.14.1 If yes, please attach a SOP for the governance and storage of samples for future use with the protocol submission.		

5.15 Will data and/or samples obtained in this study be shared with other researchers and/or institutions?	Yes	✓ No
5.15.1 If yes, please specify who will have access to data and/or samples from this study.		
5.15.2 If yes, has a Material Transfer Agreement been approved by the Research Contracts & Innovation (RC&I) office?	Yes	✓ No

Note: **All Material Transfer Agreements (MTA's) for incoming and outgoing data and/or samples should be approved by the Research Contracts & Innovation (RC&I) office and submitted to the HREC office for acknowledgment.**

5.16 What measures will be taken to protect individual privacy and the confidentiality of data?

Please see related SOPs for guidance: Privacy and Confidentiality and Collection and Storage of Data or Biological Specimens for Research Purposes

Data will be stored on REDCap data based and only access via password protection ,ensuring only study investigators will be able to access the data .

6. Clinical trials	**Is this protocol a clinical trial (tick ✓):**	☐ Yes ✓No (If no, please go to **Q.7**)

This section must be completed **only** if the research involves a clinical trial of drugs/ medicines, herbal, complementary indigenous therapies; or a substance testing a clinical outcome, therapeutic devices; an innovative therapy or intervention; off-label use or a departure from standard treatment or care.

The SA GCP Guidelines (2006) define a clinical trial as any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy.

WHO: 'a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.'

6.1 Is the product registered with the South African Health Products Regulatory Authority (SAHPRA)? (tick ✓)	☐ Yes	☐ No
If yes, please provide the registration number		
If no, is the SAHPRA' s approval letter for use of an unregistered medicine attached? Note: HREC approval must be obtained prior to study commencement.	☐ Yes ☐ Application submitted	☐ No
If registered, will the product be studied for an **indication** different to that in the latest approved SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **dose** different to that in the latest approved SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **formulation** different to that in the latest approved SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using **a route of administration** different to that in the latest approved SA package insert?	☐ Yes	☐ No

Note: If yes to any of the above, SAHPRA approval is required.

6.2 Does the study involve an FDA-monitored product (drug, device or biological)? (tick ✓)	☐ Yes	☐ No

6.3 Is this trial registered with the South African Clinical Trial Register?	☐ Yes	☐ No
If yes, please provide the registration number		
If no, application submitted?	☐ Yes	☐ No
If no application submitted, please justify.		

6.4 Is this trial registered with the Pan African Clinical Trials Registry? (See: www.pactr.org)	☐ Yes	☐ No
If yes, please provide the registration number		
If no, application submitted	☐ Yes	☐ No
6.5 Does this trial comply with the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd Edition, 2006? (tick ✓)	☐ Yes	☐ No

If no, please justify	

6.6 Note: **The Helsinki Declaration states: '*The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention.*' Please describe the local and international standards of care. If appropriate, please provide a strong justification for including an intervention in this study that is different from the recognized standard of care.**

6.7 Care after research
Please provide information about the provision of appropriate care or benefits after the study has been completed. Note: In accordance with the Helsinki Declaration of 2013, this must include provision of the investigational product once the study has been completed, for participants that benefit, or a justification as to why investigational product will not be provided. Where relevant, consent forms should include specific information clarifying what post-trial care will be provided at the end of the study, including access to any investigational products used. If none will be provided, this should also be explicitly indicated in the consent forms.

7. Statement of conflict of interest

The PI is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the PI's spouse or domestic partner and dependent children. **Please tick ✓ all that apply.**	
7.1 No conflict of interest declared:	
I, or any member of my immediate family, **do not** have any interest related to this research (e.g. financial interest in the sponsor of the research or intervention being tested.)	X
I, or any member of my immediate family, **do not** have a proprietary interest in the product being tested in this research (e.g. patent, trademark, copyright, licensing agreement).	X

I, or any member of my immediate family, **do not** have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of sponsor-investigator.	X
I, or any member of my family or business partnerships, **will not** receive any payment for enrolling participants in this study.	X

7.2 Conflict of interest declared:	
As Principal Investigator of this research **I am aware of a potential conflict of interest**. Please describe and provide a plan to manage the conflict of interest in the space below:	

8. Declarations and signatures

This application will not be processed unless all the required declarations and signatures are completed according to the Committee's Standard Operating Procedures. (see: SOP)

8.1 Head of Department or Division

My signature confirms that:

i. The researcher(s)/student(s)/supervisor(s) have the skills, training (including research ethics training), experience and time to undertake this research.
ii. There are adequate resources (e.g. equipment, space, support services) to perform this research.

Signature of Head	Signed by candidate	Date	19/11/2020
Print name	Prof Vernon Louw		

Note: Where the PI is also Head of Department, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.2 Chairperson of the Departmental Research Committee (DRC)

My signature confirms that:

i. This research protocol has undergone peer review by a person(s) experienced in the field of study.
ii. This research is well-designed and scientifically sound.
iii. Where relevant, all methodological issues have been resolved to the satisfaction of the peer reviewer(s).
iv. If conducted according to the protocol, this research is expected to yield valid and useful findings.

Signature of Chairperson	Signed by candidate	Date	19 Nov 2020
Print name	J Peter		

Note: Where the PI is also the Chairperson of the DRC, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.3 Principal Investigator

My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after written HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements stipulated in the HREC's Standard Operating Procedures; as well as national and international guidelines/regulations.
v. I will provide annual progress reports to the HREC as requested, including a final closing report at the end of the research.
vi. I will notify the HREC in writing if any change to the research is proposed and await approval before proceeding with the proposed change except when urgently necessary to protect participants' safety.
vii. I will notify the HREC in writing immediately if any adverse event or unanticipated problem occurs during the research.
viii. I will allow an audit of my research if requested by the HREC.
ix. I have the time, training, experience and resources to oversee this research.
x. I will endeavour to publish and disseminate the findings of the study.

Signature of Principal Investigatc	Signed by candidate	Date	18/11/2020
Print name	Estelle Verburgh		

8.4 Student supervisor (if research is for a degree)

My signature confirms that:

i. The student researcher has adequate training and resources to complete the research in the allocated timeframe.
ii. The research has scholarly merit.
iii. The level of risk inherent in the study is commensurate with the student researcher's experience and the extent of oversight that I will provide.
iv. I have time, training, experience and resources to oversee this research.
v. I will meet the student on a regular basis to monitor progress and address any problems that may arise during the study.
vi. I will ensure that the research undergoes continuing review as required by the HREC, including annual progress reports, protocol amendments and a final closing report at the end of the research.
vii. If applicable, I will ensure that I report unanticipated problems or serious adverse events to the HREC.
viii. I will arrange for an alternative faculty supervisor to take responsibility for this research during periods of absence such as sabbatical or annual leave.

Signature of Supervisor	Signed by candidate	Date	18/11/2020
Print name:	Estelle Verburgh		

Note: The supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

8.5 Student (if research is for a degree)

My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after written HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements as stipulated in the HREC's Standard Operating Procedures.

Signature of Student		Date	16/11/20
Print name	Dr E **Adams**		

HREC - Debit Order Form

Please complete the Ethics Debit form if you ticked off between b - g.

To be Completed by the Ethics Office:

Reference number of Study: _____ Date: _____

Name of Person Completed: _____ Signature: _____

Research Ethics Committee Fee Structure – New Application		
Submission Type - Description	**New fee (Vat Incl.)**	Tick Appropriate Box for billing
New Clinical Trial - Pharmaceutical / Industry driven company sponsors an investigator to conduct a new research project	**R 31 993.00**	☐
International grant funded research (Total project budget above R5m)	**R 22470.00**	☐
International grant funded research (Total project budget R1m to R5m)	**R 14980.00**	☐
International grant funded research (Total project budget below R1m)	**R 7490.00**	☐
National grant funded research (Total project budget >R1m)	**R 3600.00**	☐
Extension clinical study / Additional clinical site	**R 15000.00**	☐

Please note completion of this form is crucial and must be included in all the Submissions submitted

Section A: Fund Deduction	
Project name	
Principle Investigator – (PI)	
Fund Number & Cost Centre	
Fund Holder	
Contact Person for payment queries	
Contact number for payment queries	
Amount to be deducted: (Refer to Addendum A – attached Fee Structure)	R

Note: If fund provided **has insufficient funds, a miscellaneous fund will be allocated automatically.**

If fund is not applicable and Sponsor should be billed, Please complete Section B.

Section B: Sponsor Details / Biller to be invoiced directly	
For invoices to be generated correctly, kindly complete below:	
Sponsor's name	
Contact person	
Address	
Vat number	
Telephone number	
Email Address	
Amount to Be Billed (Refer to Addendum A – attached Fee Structure)	R

New protocol submission checklist

Please ensure that all the applicable sections are fully completed and included in the submission. Missing information will delay the review process as the application will be returned to the PI. Sections A-C must be included. Instructions for submission of new applications are posted on the HREC website.

Note: There are two categories for submissions of studies – those that are reviewed by the full HREC committee and those that are expedited i.e. are reviewed outside the full HREC meeting.
Upon receipt of the protocol application, an assessment of the likely risks to participants will be undertaken and a decision will be made by the HREC EXCO as to whether a protocol may be expedited. **All expedited protocols are still subject to full review; and are not subject to any timeline advantage.**

Category 1: For Industry/ Pharmaceutical / Grant / Donor Sponsored Clinical Trials involving Drugs / Devices

Instruction for full committee review:

- Please submit 3 hard copies of your submission pack for full committee approval.
- Please prepare your submission pack in the order specified below.
- Please separately add **10** copies of the PI Generated Synopsis & Sponsor's Synopsis (all copies to be stapled)
- Please separately add **10** copies of the Informed Consent Forms (all copies to be stapled)
- Please email the Synopsis, consent forms and protocol for full committee to hrec-enquiries@uct.ac.za)

Category 2: For Expedited Studies

Protocols may be potentially reviewed using an expedited review process if they meet the following criteria [45 CFR 46.110(b)(1)]:
a. Research poses no more than minimal risk to subjects; AND
b. Research for which each of the procedures falls within one of the following expedited review categories outlined by the Office for Human Research Protections (OHRP) [45 CFR 46.110] and the Food and Drug Administration (FDA) [21 CFR 56.110]: Eligibility for Expedited Review of US Federally-funded Research – Pointers for Researchers. Also see see 'eligibility for expedited review' in the HREC SOP for the Protocol Review Process).

Instruction for expedited review:

- Please submit 2 hard copies of your submission pack for review. (Please email a copy to hrec-enquiries@uct.ac.za)
- Please prepare your submission pack in the order specified below.
- Please motivate fully for an expedited review using the eligibility criteria above
- Please note that after receiving your submission, the HREC Chairperson or designee might determine that your study falls in more than minimal risk to subjects and does require full committee review. the HREC Office will request additional copies of the documents for circulation among Committee members before the next HREC meeting.

Note: For our scanning purposes we request that you please refrain from binding the documents. Please don't use binder files where holes are punched in the documents. Please use binder clips or staples to secure documents. Please avoid using ring binders.

Please pack 3 copies for category 1 and 2 copies for category 2 in the order specified below:
Note: **Submissions will be sent back when insufficient copies are provided.**

For Full Committee Review (3 copies) Category 1		**For Expedited Review (2 copies) Category 2**
1. Completed Protocol Application Form		1. Completed Protocol Application Form
2. Cover letter listing all submitted docs with version numbers and version dates		2. Cover letter listing all submitted docs with version numbers and version dates
3. PI Generated Synopsis (see FHS014) (Required)		3. PI Generated Synopsis (see FHS014) (Required)
4. Debit Form (Required)		4. Debit Form (Required)
5. Sponsor's Synopsis (if applicable)		5. Motivation for Expedited Review
6. Research Protocol (see FHS015hlp)		6. Research Protocol (see FHS015hlp)
Appendices (as applicable)		Appendices (as applicable)
7. Consent and assent forms (English versions)		7. Consent and assent forms (English versions)
8. Sponsor's Protocol		8. NIH or other US federal grant application (if PI is primary awardee)
9. NIH or other US federal grant application (if PI is primary awardee)		9. Surveys, questionnaires, interview schedules
10. If an application has been submitted to the SAHPRA, a copy of (Ethical Issues) extracted from the CTF1 application form		10. Recruitment materials: advertisements, flyers, posters
11. Surveys, questionnaires, interview schedules		11. Materials for participants: diaries, patient identification cards
12. Recruitment materials: advertisements, flyers, posters		12. Letters of authorisation from institutions such as hospitals, clinics and schools
13. Materials for participants: diaries, patient identification cards		13. Insurance Certificate (where applicable)
14 Letters of authorisation from institutions such as hospitals, clinics and schools		14. Budget summary
15. Post-trial care/Care after research justification		15. Other relevant documentation
16. A summary of Phase III efficacy and safety data if this is an application for an open label or extension study		15. Post-trial care/Care after research justification
17. Insurance Certificate		16. If Minors are involved, please attach FORM A found on the website
18. Budget summary		17. SOP for governance and storage of samples; and MTA's (where applicable)
19. SAHPRA letter of approval, if available		
20. Investigator's brochure and package inserts		
21. In the case of clinical trials, PI's declaration, CVs and GCP certificates for PI and co-investigators		
22. If Minors are involved, please attach FORM A found on the website		
23. SOP for governance and storage of samples; and MTA's (where applicable)		
24. Other relevant documentation		

Note:

- Clearly list all documents with version numbers and dates on the cover letter.
- For our scanning purposes we request that you please refrain from binding the documents. Please don't use binder files where holes are punched in the documents. Please use binder clips, paper clips and staples. Please avoid using ring binders.

Please submit the completed form together with the supporting documents by hand delivery or registered mail to	**FHS Human Research Ethics Admin Office** **c/o the secretary – HREC Office Address:** Human Research Ethics Committee E 53, Room 46, Old Main Building, Groote Schuur Hospital, Observatory Office Contacts: 021 406 6492; 021 404 7682; 021 406 7260 Electronic copy of your submission to be emailed to: hrec-enquiries@uct.ac.za Invoice queries: shakirah.coenraad@uct.ac.za **Website:** http://www.health.uct.ac.za/fhs/research/humanethics/forms/

SYNOPSIS

Lymphoma is amongst the top 10 most common malignancies, globally. Lymphoma presents with variable symptoms and is often overlooked in tuberculosis (TB) endemic areas like South Africa (SA) as both conditions present similarly. Typical symptoms of both conditions include constitutional symptoms such as fever, weight loss, night sweats and lymphadenopathy. A delay in diagnosing lymphoma has been associated with advanced disease at the time of presentation and an increased mortality rate. The main driver of delayed diagnosis is the healthcare practitioner interval; the time between when a patient first makes contact with the health practitioner and the time of diagnostic biopsy. The high HIV burden in SA furthers contributes to the diagnostic delay of lymphoma. This is because most HIV-infected patients presenting with constitutional symptoms are misdiagnosed and started on TB treatment. This highlights the importance of an accurate diagnostic pathway for both TB and lymphoma.

Abdominal ultrasound has been included in the World Health Organization's (WHO) algorithm for seriously ill HIV-infected patients with suspected extrapulmonary TB. As such, patients presenting with overlapping TB and lymphoma symptoms often receive an abdominal ultrasound. However, with more advanced scans forming the back bone of the lymphoma diagnostic imaging pathway, there is a paucity regarding specific lymphoma features visible on an abdominal ultrasound. The primary aim of the proposed study is, therefore, to evaluate the diagnostic accuracy of abdominal ultrasounds in the diagnostic pathway of patients presenting to a lymph node biopsy clinic. This will be achieved by the following objectives: (A) we will review the probable diagnosis made by physicians referring patients to the lymph node biopsy clinic as well as which other tests preceded referral for biopsy. (B) We will describe the frequency of specific echo-graphic abnormalities of lymph nodes, spleen, liver and free fluid. (C) We will determine the relationship between the findings and differential diagnoses derived from abdominal ultrasounds and the findings and diagnoses made based on lymphadenopathy aspirates and biopsies.

The study population will comprise patients referred to the peripheral lymph node biopsy clinic at E5 Haematology Clinic, Groote Schuur Hospital, between 2017 and 2020, who also received an abdominal ultrasound within six months of their biopsy date. All of these patients are older than 18 years of age and we will include this entire population. The research will take the form of a retrospective cross-sectional study, using patient records and previously collected data. Patients will be identified using the already available lymph node biopsy clinic E5 REDCap database. All patients have already provided informed consent to be included in this database. Diagnostic and clinical data will be obtained from the REDCap database while details relating to their abdominal ultrasound will be obtained using their folder number/name on the Radiology PACS system.

All data used in this study will be stored in a UCT secured REDCap database. Computer-based records will only be available to the study investigators using access privileges and passwords. Personal identifiers will be removed when data is extracted into excel for analysis. There is no risk to patients in this retrospective review and the potential benefit will be increased knowledge on the diagnostic pathway of lymphadenopathy and the role of abdominal ultrasounds.

DIVISION OF CLINICAL HAEMATOLOGY, DEPARTMENT OF MEDICINE
CLINICAL RESEARCH OFFICE
Room E4-68, E5 Haematology New Main Building
Groote Schuur Hospital
Observatory, 7925
Cape Town, South Africa
Tel: +27 (0) 21 404 3070/80 Fax: +27 (0) 21 4043088
E-mail Research Coordinator: jenni.coetsheer@uct.ac.za
E-mail Research Supervisor: estelle.verburgh@uct.ac.za
E-mail Head of Division: vernon.louw@uct.ac.za

16 November 2020

Human Research Ethics Committee
E52, Room 24
Old Main Building
Groote Schuur Hospital
Observatory

Dear HREC committee, Prof Blockman,

RE: MOTIVATION FOR EXPEDITED REVIEW

Protocol Title: A retrospective cross-sectional study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a high HIV TB endemic population

Principal Investigator: Prof. Estelle Verburgh
MMed Student: Dr Ellouise Chantel Adams

I hereby submit my proposal for expedited review.
The study meets the criteria for expedited review as motivated below:

- As per UCT HREC criterion: *'No more than minimal risk to subjects.'*
- Previously diagnosed patients will be identified and included for retrospective review...
- The patients have been retrospectively and prospectively included in the E5 Haematology Database HREC R024/2018
- There will be no direct involvement with human participants, and there will not be an informed consent process.
- The study therefore poses no risk of discomfort or harm to participants.

Kind regards,

Signed by candidate

Dr Ellouise Chantel Adams

Signed by candidate

Prof. Estelle Verburgh

A retrospective cross-sectional study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a high HIV TB endemic population

Dr Ellouise Chantel Adams

In fulfilment of the requirements for the degree
Master of Medicine (MMed) in Medicine

Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Date of Submission: November 2020

Supervisor: Prof E Verburgh
Department of Medicine
University of Cape Town

TABLE OF CONTENTS

TITLE

A retrospective cross-sectional study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a high HIV TB endemic population.

BACKGROUND

Lymphoma is amongst the top 10 common malignancies worldwide(1).Lymphoma can present with variable signs and symptoms. It is commonly overlooked in tuberculosis (TB) endemic areas, like South Africa (SA), as lymphoma and TB present with overlapping symptoms. Typical presentation of lymphoma includes lymphadenopathy and B symptoms – a history of >10 % weight loss in 6 months, night sweats and a temperature of >38°C. These symptoms are identical to constitutional symptoms experienced by patients suffering from TB. As such, diagnosing lymphoma in a TB endemic area is difficult(2).

A delay in diagnosing lymphoma in sub-Saharan Africa has been associated with advanced disease at the time of presentation and an increased mortality rate(3). The primary contributing factor to delayed lymphoma diagnosis is the health practitioner interval(3).This interval can be defined as the time between when a patient first makes contact with the health practitioner and the time of diagnostic biopsy. When comparing average specialist referral time in SA to the United Kingdom (UK), SA has a diagnostic delay of approximately 5 -7 weeks. The UK National Institute for Health and Care Excellence (NICE) guideline has a target of a specialist referral within 2 weeks of suspected lymphoma and a biopsy within 2-3 weeks. In SA a median time of 7 weeks to diagnose lymphoma has been observed, highlighting the importance of improving the healthcare professional's ability to detect and adequately refer a suspected lymphoma patient.(3)

Another contributing factor to the diagnostic delay of lymphoma in SA, is the high HIV burden. Most HIV-infected patients presenting with lymphadenopathy and constitutional symptoms, are started on empirical TB treatment(3, 4). Empirical TB treatment delays the time to diagnosis of lymphoma by a median of 4 weeks. As such, a large group of lymphoma patients are misdiagnosed with TB. As a result of delayed diagnosis and incorrect

diagnoses/treatment, we need a more accurate diagnostic pathway for both TB and lymphoma(5, 6).

Abdominal ultrasound has been included in the World Health Organization's (WHO) algorithm for seriously ill HIV-infected patients with suspected extrapulmonary TB(7). This diagnostic tool is easily accessible and widely available. With the increase in popularity of the point of care ultrasound, bed side point of care ultrasound has become a pertinent test during admission and workup of sick patients. Abdominal ultrasound features suggestive of extrapulmonary TB include: (i) splenic hypoechoic lesions, (ii) lymph nodes >10mm in length and (iii) abdominal/pleural/pericardial effusions. These features are all independent predictors of TB(8).

A recent study showed that 66% of participants with culture positive TB had at least one or more of these three features. Moreover, the combination of all three of these features are highly suggestive of extrapulmonary TB(8). Patients presenting with overlapping TB and lymphoma symptoms often receive an abdominal ultrasound at their initial presentation visit. However, with CT and nuclear medicine scans forming the back bone of the lymphoma diagnostic imaging pathway(9), there is a paucity regarding specific lymphoma features visible on abdominal ultrasound.

RESEARCH QUESTION & HYPOTHESIS

Research question:

What is the relationship between abdominal ultrasound findings and the final diagnosis made at a lymph node biopsy clinic between 2017 and 2020?

Hypothesis:

We hypothesize that abdominal ultrasound features are not associated with the final diagnosis made on lymph node cytology and histology.

AIMS & OBJECTIVES

Aim:

The primary aim of this study is to evaluate the diagnostic accuracy of abdominal ultrasounds in the diagnostic pathway of patients presenting to a lymph node biopsy clinic at Groote Schuur Hospital.

Objectives:

i) To review the probable diagnosis made by physicians referring patients to the lymph node biopsy clinic as well as which other tests such as chest X-ray and lymph node aspirate, preceded referral for biopsy.

ii) To describe the frequency of a set of specific echo-graphic abnormalities of lymph nodes, spleen, liver and free fluid.

iii) To determine the relationship between the findings and differential diagnoses derived from abdominal ultrasounds and the findings and diagnoses made based on lymphadenopathy aspirates and biopsies.

STUDY DESIGN

This research will take the form of a retrospective cross-sectional study using data from patient hospital records and data previously collected as part of the RADLAC study (HREC:647/2017), stored in the lymph node biopsy clinic E5 REDCap database.

STUDY POPULATION & SETTING

The study population will consist of patients referred to the peripheral lymph node biopsy clinic at E5 Haematology Clinic, Groote Schuur Hospital who also received an abdominal ultrasound. These patients all presented to a primary healthcare professional with peripheral lymphadenopathy and were referred to the clinic between 2017 and 2020. Figure 1 below shows the flow of participants through the study.

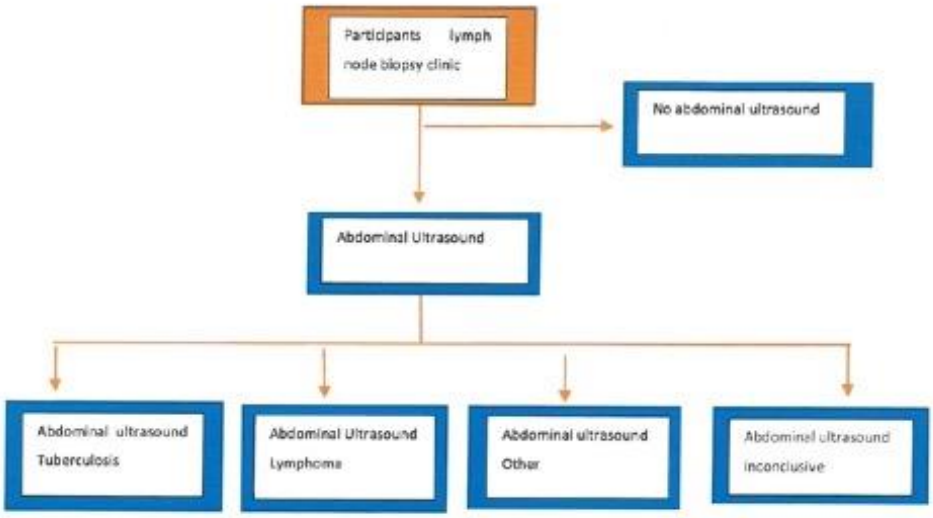

Figure 1. Diagram to report flow of participants through the study

INCLUSION & EXCLUSION CRITERIA

Inclusion criteria:

This study will include patients who:

(i) had a lymph node biopsy at the E5 lymph node biopsy clinic between 2017 and 2020

(ii) received an abdominal ultrasound within six months of referral for biopsy

(iii) provided consent to be included in the RADLAC study

No restrictions will be made based on HIV status.

Exclusion criteria:

All patients who fulfilled the above criteria will be included with no exclusions.

RECRUITMENT AND ENROLMENT

Patients who also had an abdominal ultrasound will be identified from the already available lymph node biopsy clinic E5 REDCap database.

RESEARCH PROCEDURES AND DATA COLLECTION METHODS

This is a retrospective cohort study that will make use of patient records and previously collected data. The diagnostic and clinical data of patients enrolled into the lymph node biopsy clinic will be obtained from the lymph node biopsy clinic E5 REDCap database. Details relating to their abdominal ultrasound will be obtained using their folder number/name on the Radiology PACS system.

ANALYTIC CONSIDERATIONS

Sample size:

We estimate that around 50 of the 200 patients evaluated at the lymph node biopsy clinic between 2017 - 2020, received an abdominal ultrasound within six months of their lymph node biopsy. This entire population will be included in the study.

Data management & quality assurance:

The lymph node biopsy clinic E5 REDCap database is secured behind a firewall and is password protected. The database has built in quality assurance features. REDCap Data Quality module, which allows for real-time execution of pre-defined and custom-built rules to check for discrepancies in the data. Pre-defined rules include missing values, data out of range, outliers for numerical fields, multiple choice fields with invalid values and incorrect values for calculated fields. Additional data collected from patient records will be added to this secure database.

Data analysis:

Data will be exported into STATA V14 (Stata Corporation, College Station, Texas, USA) where it will be analysed. Patient characteristics will be described by frequencies (%), means and standard deviations or medians and interquartile ranges, as necessary. Tests of association will be used to estimate the relationship between abdominal ultrasound diagnoses and lymph node biopsy histology and cytology diagnoses, as appropriate. For all analyses, statistical significance will be set at α=0.05.

Variables for descriptive analysis will include:

- age
- gender (male vs female)
- HIV status and related parameters (CD4 count, viral load, anti-retroviral therapy)
- biopsy site
- indication for ultrasound
- date ultrasound performed
- date patient enrolled in the study

Ultrasound parameters that will be reviewed include:

- hepatomegaly
- hepatic lesions
- lymph nodes seen and size,
- location of lymph nodes
- presence of ascites or pleural effusion,
- splenomegaly
- splenic microabcesses
- differential diagnosis made by ultra-sonographer.

Lymphadenopathy investigations for analysis include:

- aspirate cytology
- lymph node histology
- Xpert Ultra findings on aspirate and biopsy
- Final diagnosis made of lymphadenopathy.

Table 1: table comparing abdominal ultrasound diagnosis with histologic and cytological diagnosis of lymph node biopsy

	Lymph node biopsy Histology and cytology diagnosis			
Abdominal ultrasound final diagnosis	Tuberculosis	Lymphoma	Other	Inconclusive
Tuberculosis	a	e	I	m
Lymphoma	b	f	j	n

Other	c	g	k	o
Inconclusive	d	h	l	p

ETHICAL CONSIDERATIONS

Ethical review:

This protocol will be submitted to the UCT Departmental Research Committee and the UCT Human Research Ethics Committee.

Informed consent:

All patients gave informed consent to be included as subjects in the RADLAC study cohort (consent form attached).

Risks & benefits to participants:

There is no risk to patients in this retrospective review and the potential benefit will be increased knowledge on the diagnostic pathway of lymphadenopathy and the role of ultrasound abdomen.

Privacy and confidentiality:

The data has been and will be collected and recorded into the UCT secured password protected ES lymph node biopsy clinic REDCap database. Computer-based records will only be available to the investigators involved in the study using access privileges and passwords. Personal identifiers will be removed when data is extracted for analysis .

What happens at the end of the study?

The findings of this study will be written up in the form of an article and will be submitted to a peer-reviewed medical journal for publication.

COSTS

No funding required.

TIMING

• The protocol will be submitted to the Departmental Research Committee in November 2020 and to the UCT Human Research Ethics Committee before 31 December 2020

• Data analysis will be completed by February 2021

• Manuscript preparation and completion will be accomplished by June 2021 for submission for publication

REFERENCES

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2. Cain KP, Varma JK. You have to find TB to treat TB. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(7):854.
3. Antel K, Levetan C, Mohamed Z, Louw VJ, Oosthuizen J, Maartens G, et al. The determinants and impact of diagnostic delay in lymphoma in a TB and HIV endemic setting. BMC cancer. 2019;19(1):384.
4. Saranchuk PB, A.; Hilderbrand, K.; Coetzee, D.; Bedelu, M.; van Cutsem, G.; Meintjes G. Evaluation of a diagnostic algorithm for smear-negative pulmonary tuberculosis in HIV-infected adults. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2007(97):517-23.
5. Antel K, Oosthuizen J, Malherbe F, Louw VJ, Nicol MP, Maartens G, et al. Diagnostic accuracy of the Xpert MTB/Rif Ultra for tuberculosis adenitis. BMC infectious diseases. 2020;20(1):33.
6. Antel K, Louw VJ, Maartens G, Oosthuizen J, Verburgh E. Diagnosing lymphoma in the shadow of an epidemic: lessons learned from the diagnostic challenges posed by the dual tuberculosis and HIV epidemics. Leukemia & lymphoma. 2020:1-5.
7. Organization WH. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach: World Health Organization; 2016.
8. Van Hoving DJ, Griesel R, Meintjes G, Takwoingi Y, Maartens G, Ochodo EA. Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. The Cochrane database of systematic reviews. 2019;9:Cd012777.
9. Verburgh E, Antel K. Approach to lymphoma diagnosis and management in South Africa. South African Medical Journal. 2019;109(10).

PART 2: CERTIFICATE OF CONSENT

I have read the participant information leaflet, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Or thumb print if unable to sign

Date _____

(dd/mmm/yyyy)

If unable to read or write
An impartial witness who is able to read and write must sign (if possible, this person should be selected by the participant and should have no connection to the research team).

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____

Signature of witness _____

Date _____

PART 3: STATEMENT BY THE RESEARCHER/PERSON TAKING CONSENT

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Fine needle aspiration of the lymph node
2. Core biopsy of the lymph node if inadequate material aspirated
3. Excision biopsy of the lymph node if core biopsy is non-diagnostic
4. A blood test for a CD4 count if this is not available from the clinic in the preceding 6 months

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided/ offered to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____

University of Cape Town
Faculty of Health Sciences

Memorandum of understanding

between

postgraduate student and supervisor

This memorandum of understanding between

...(name of graduate student) Dr Ellouise Adams
....(signature)
(date) 08/11/20 Signed by candidate

and

....(name of supervisor) A/Prof Estelle Verburgh
(signature)
....(date) 18/11/2020 Signed by candidate

is designed to ensure that the supervision experience is as mutually productive as possible.

(This must be completed within six months of initial registration; an annual **progress and planned activity** report must be completed each subsequent year before the student renews his/her registration)

Candidate details:

A1 Name of Candidate: Dr Ellouise Adams Student number: admell003

A2 Highest academic qualification: MBhCB

A3 Degree registered for: M x PhD ___ Year of first registration: 2020

A4 Project title and proposal: (attach proposal separately): A retrospective cohort study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a HIV TB endemic population

The supervision arrangements:

General obligations of supervisors are outlined in appendix I. By signing this document, both parties acknowledge their understanding of the general expectations it contains.

B1 Supervisor:

(a) Initials & surname: A/Prof Estelle Verburgh

(b) Staff no:... 01437843

(c) Department:. Medicine

B2 Co-supervisor(s) if any:

(a) Initials & surname:.

Department:....

Institution:..

Responsibilities:....

(b) Initials & surname:....

Department:...

Institution:.....

Responsibilities:.....

...

3

Outline of expectations and commitments:

C1 In free format/point form provide an outline of expectations set out in as much detail as possible to the satisfaction of supervisor and candidate (use separate pages if necessary).

Research expectations: *(laboratory access; field work; access to equipment; courses to attend; conference attendance; seminar presentations)* ..

..... Complete protocol, data collection, analysis, write up and submission

Supervisor/student commitments (*access to supervisor; annual leave for student; working hours; data ownership[1]; patents*; (co)authorship of articles):*

.. Have regular meetings with supervisor regarding progress of the above

.. Both student and supervisor will be co-authors on manuscript

..

..

..

..

..

Financial support: *(stipend; research costs; conference and travel, etc):* ....

.. none

..

Observation by Head of Department

I have reviewed this completed MoU and I am satisfied that the department is able to meet the obligations to the candidate as set out in this MoU:

Signed:.

Name:...

Date:.

I approve registration of the candidate in the Faculty of Health Sciences:

Signed:

Dean/Deans nominee

Name:..
Date:

See Supervision Booklet for UCTs IP policy

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

GUIDELINES FOR THE APPOINTMENT OF SUPERVISORS OF DOCTORAL AND MASTERS CANDIDATES

REQUIREMENTS

1. Every doctoral (PhD) or masters candidate must have a Faculty of Health Sciences approved supervisor, and may also have one or more co-supervisors *(applies also to dissertation component of course-work Masters programmes)*.

QUALIFICATIONS OF SUPERVISORS

2. Senate must appoint a suitably qualified person to be the supervisor. While Senate allows the possibility of the appointment of a person who himself/herself does not have a doctoral qualification, for such a person to be nominated or appointed for a PhD candidate there must be evidence of research, research supervision, and strong motivation. Having a PhD is however not sufficient proof that a person is suitable for appointment, but is an indication which with other evidence may be conclusive.

SUPERVISORS AND CO-SUPERVISOR(S)

3. In many cases one or more co-supervisor may be appointed on the advice of the Faculty concerned to direct the work of an Masters or PhD candidate. The policy of the Faculty of Health Sciences is that every Masters or PhD candidate must have a UCT supervisor. He/she may also have a co-supervisor, or more than one, and the co-supervisor(s) may be external.

   Where a supervisor has left UCT but is willing to continue to supervise, he or she may be appointed as co-supervisor and a supervisor who is internal to UCT must be appointed.

4. An Emeritus Professor may to continue as supervisor after retirement where the Emeritus Professor has a continuing formal relationship with UCT.

5. The role of each co-supervisor must be clearly demarcated at the outset of the research programme and the candidate must be fully informed about the respective roles of the supervisor and any co-supervisor(s).

RESPONSIBILITIES OF SUPERVISORS

6. The supervisor must have demonstrated an interest and expertise in the field of the candidate's research. The supervisor must not undertake to supervise students in fields or on topics in which he/she has no expertise or interest.

7. ***The supervisor must recognise that accepting a research student involves a commitment to see a project through to completion within the Faculty's normal time parameters (3 years for Masters ; 4 years for PhD).***

   (a) The supervisor must be a member of the University staff. *(Note: A modest honorarium is payable to co-supervisors who are not members of UCT staff.)*

   (b) In the absence of a supervisor for a substantial period, adequate provision must be made by the Head of Department for continuing supervision, if necessary by appointing an acting supervisor.

8. The supervisor must be familiar with the rules governing the degree, and must be able to advise the candidate in matters relating to the rules.

9.

5

The supervisor(s) must, during the initial stages of the students tenure in the Department, discuss the principles with respect to authorship of publications emanating from the work the student is to be involved in. In particular, the students and supervisors expectations with respect to the potential order of authorship must be discussed openly. The principle that the order of authorship should be decided according to the relative contribution of each potential author and that this should be a joint decision of all the authors, must be considered.

10. If the candidate is not writing in his/her home language, the supervisor must assess at an **early stage** whether any special assistance (which cannot be provided as part of normal supervision) might be needed and make the necessary arrangements with the department or other appropriate bodies.

11. The supervisor must ensure that candidates for research projects are fully aware of the UCT Code of Ethics for researchers and where necessary obtain any ethical clearance required.

12. The supervisor must not permit a student to work on a project if any doubt exists about the availability of adequate material, records or equipment.

13. The supervisor should assist the candidate by:

(a) advising candidates on drawing up a schedule which details the completion dates of different stages of the project;

(b) assisting with the management of this schedule;

(c) providing information relating to relevant literature and sources;

(d) putting the candidate in touch with researchers working in related fields;

(e) discussing and critically evaluating the candidate's findings and ideas;

(f) promptly reading, criticising and annotating draft chapters;

(g) advising the candidate on the form and structure of the thesis;

(h) ensuring that the candidate is (or becomes) familiar with, and observes one of the internationally recognised guides to scholarly convention, presentation, documentation of sources and the like;

(i) referring the candidate to approved style manuals;

(j) ensuring that the candidate is aware that **plagiarism** is a serious offence that will be dealt with in terms of the University disciplinary rules, and that the University has effective means of detecting plagiarism, especially that arising from the use of the internet and other electronic sources.

14. The supervisor must not attempt to impose his/her own stamp, theoretical or stylistic, on the candidate's work.

15. The supervisor and candidate must meet sufficiently frequently to ensure that progress is not slowed down for want of constructive advice and criticism.

16. The supervisor must insist on seeing drafts of major sections of the thesis (or extended essay) as it is written. The supervisor must respond as quickly as possible to the written submissions of the students.

17. Although a candidate may submit for examination without the approval of the supervisor, the supervisor must see a complete draft before submission.

18. Towards the end of each academic year, the supervisor must report to the relevant Faculty Board on the progress of each student (via the Progress and Planned Activity report form) and make recommendations regarding re-registration the following year.

D3 Appointment of supervisor

Name and student no of proposed candidate:	Ellouise Adams admell003
Degree name (e.g. MSc(Med) in Physiology)	MMed

Name of Supervisor/co-supervisor	A/Prof Estelle Verburgh
UCT staff number	01437843
UCT Academic Department	Internal Medicine
Division	Heamatology
Permanent or contract staff? If contract, when did your contract start and when will it end?	Permanent
Educational Qualifications	MD PhD
Are you registered with a Professional Council in SA?	Yes
If yes, in what category?	Medical practitioner
Please provide Council/Professional body registration number	0368431
Have you previously supervised a candidate at this level?	Yes
How many students are you currently supervising/co-supervising?	7
If yes, how many and at what level?	PG Diploma: Honours: Masters: 5 Doctoral: 2
If none, then please provide a brief motivation for doing so now. *HOD please state the arrangements for mentoring of the novice supervisor*	
Have you previously submitted a CV or resume to the postgraduate office? If not, then please attach a recent CV or resume	Yes

Supervisor/co-supervisor signature: Signed by candidate Date: 19/11/2020

I approve/ do not approve the appointment of the above-named supervisor/co-supervisor

HOD name: _____

HOD signature: _____ Date: _____

I approve/ do not approve the appointment of the above-named supervisor/co-supervisor

Deputy Dean: Postgraduate Affairs

Signature: _____ Date: _____

Form D3 - 2007

Departmental Research Proposal Checklist

Name of Applicant: Dr Ellouise Adams

1. Degree registered for: Master of Medicine

2. Year of first registration: 2020

3. Project Title: A retrospective cross-sectional study of the abdominal ultrasound findings of patients evaluated for peripheral lymphadenopathy in a high HIV TB endemic population

4. The protocol was presented at a unit/research group/division/Department meeting

   Yes No √

If yes

Details of the seminar/meeting:

Academic staff present:

5. The protocol has been reviewed by the following two independent staff members not involved with the study:

	Reviewer 1	Reviewer 2
Name	Prof Vernon Louw	Dr. Cecile du Toit
Signature	Signed by candidate	
Date	19/11/2020	19/11/2020

6. The principal and co-investigators have read and approved all the documents included in the application:

	NAME	SIGNATURE
Supervisor	**Prof Estelle Verburgh**	Signed by candidate
Co-supervisor		
Co-supervisor		
Co-supervisor		
Co-supervisor		

7. Ethics consideration:

Animal Ethics is already approved* still needs to be applied for ✓not applicable

Human Ethics is already approved* √still needs to be applied for not applicable

* If the research project already has ethical approval, please attach the HREC approval letter and the research protocol.

8. The following documents are attached:

	Yes	No	N/A
• Animal/Human Ethics letter of approval	☐	√	☐
• Research Proposal	√	☐	☐

If not, please give an explanation:

Protocol still to be submitted for ethical approval

9. Department Research Committee representative:

	NAME	SIGNATURE
DRC representative	J Peter	Signed by candidate

Southern African Journal of Medicine – Instructions to Authors

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
  Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.
  Research methods and design: This must address the following:
- Study design: An outline of the type of study design.

- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.
  Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

  Discussion: The discussion section should address the following four elements:
- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.
  Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

  Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

  Also provide the following, each under their own heading:
- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.

- Author contributions: All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.
  References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.